UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,554	06/28/2001	Anna Edman Orlefors	HO-P0221US0	4792

26271 7590 10/20/2003

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,554	ORLEFORS ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6,12,16 and 19-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6,12,16, and 19-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed on 7/17/2003 has been entered.

Claims 2, 4, 6, 12, and 16 have been amended, claims 1, 3, 5, 7-11, 13-15, and 17-18 have been canceled, and claims 19-31 have been added. Claims 2, 4, 6, 12, 16, and 19-31 are now pending.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 2, 20 and 21are rejected under 35 U.S.C. 102(b) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996).

Interpreting claim 1's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device.

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the steps of:

(i) forming immobilized double stranded DNA comprising one strand of sample DNA and one strand of primer DNA on one or more reaction areas in a microchannel structure of a microfluidic device(Pg. 85, bottom right see also pg. 88 bottom right where capillary use is taught). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) adding a deoxynucleotide analogue or dideoxynucleotide and a DNA polymerase to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide, deoxynucleotide analogue or dideoxynucleotide with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85-86)

(iii) detecting whether or not the deoxynucleotide, deoxynucleotide analogue or dideoxynucleotide added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

(iv) removing excess of deoxynucleotide from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these deoxynucleotides following the wash steps on page 87.

(v) repeating steps (ii)-(iv) with different deoxynucleotides, deoxynucleotide analogues or dideoxynucleotides is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".

(vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semiautomated solid-phase Sanger sequenceing"(Pg. 87, see figure 5).

With regard to claim 20, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 2, 4, 6, 12, 16, and 19-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

Interpreting claim 1's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device.

With respect to claim 2, Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA comprising the steps of:

(i) forming immobilized double stranded DNA comprising one strand of sample DNA and one strand of primer DNA on one or more reaction areas in a microchannel structure of a microfluidic device(Pg. 85, bottom right). Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) adding a deoxynucleotide analogue or dideoxynucleotide and a DNA polymerase to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added deoxynucleotide, deoxynucleotide analogue or dideoxynucleotide with the strand of sample DNA that is part of the immobilized double stranded DNA(Page 85-86)

(iii) detecting whether or not the deoxynucleotide, deoxynucleotide analogue or dideoxynucleotide added in step (ii) is added to the primer DNA in said one or more reaction areas;(Page 86).

(iv) removing excess of deoxynucleotide from one or more reaction areas; is taught throughout the Ronaghi reference in their teachings in Figure 1 and later on page 87 as they wash the beads on which the deoxynucleotides are immobilized, the reference further teaches the loss of these deoxynucleotides following the wash steps on page 87.

(v) repeating steps (ii)-(iv) with different deoxynucleotides, deoxynucleotide analogues or dideoxynucleotides is taught by Ronaghi in Figure 1 and in the text of Page 87 in their teaching that "the sequencing procedures were repeated several times".

(vi) identifying said sequence from the results of the above previous steps is obviously then taught in the reference's sequencing previously alluded to in (v) and furthermore that "the obtained sequence was confirmed by semiautomated solid-phase Sanger sequenceing"(Pg. 87).

With regard to claim 20, Ronaghi et al. teaches the above method wherein the detecting step (iii) measures the release of pyrophosphate(Page 85).

With regard to claim 21, Ronaghi et al further teach the method wherein the pyrophosphate release is detected by light emitted from a luciferin luciferase reaction(Fig. 1, Pg. 85).

But, with respect to Claims 4, 6, 12, 16, 19, and 22-31 Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved(claims 4, 12, 16, and 19) by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. Applicant should note that the examiner is assuming applicant's use of "centrifugal" to be non-intentional and that they really intended to maintain their previous claim's recitation of "centripetal", because of this assumption, the art has been applied

accordingly. Furthermore, Ronaghi et al. does not teach labeling the deoxynucleotide, deoxynucleotide analogue, or dideoxynucleotide that is added in the method.

However, Mian et al. (US Patent 6,319,469 B1) teach performing the previously taught methods of Ronaghi inside a microfluidic device. Mian et al. teach performing the steps of adding sample DNA on a reaction area in a microfluidic device(see Col. 49 lines 1-4), attaching or hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers(Col. 49 lines 2-19). Furthermore, the Mian et al. reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force(Col. 3 lines 5-25). The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a "simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological, biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids"(Col. 3 lines 5-10). The reference provides that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and

centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates high-throughput analysis for both genome sequencing and routine clinical applications "that are sophisticated(for professional, eg hospital, use), easy to use(for consumer eg at-home monitoring, uses), and portable (for field environmental testing, use)" (Col. 3 lines 19-22).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claims 6, 22, 25, 26, and 29-31 and the limitation of a fluorescently labeled dideoxynucleotide, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by spinning the disk(Col. 47 lines 15, 28, 39 for example). Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic

arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches. Mian et al. teaches the use of a terminator solution containing a dideoxynucleotide covalently-linked to a fluorescent label in Example 7, Col. 49. In addition, Mian et al. teach, in addition to the aforementioned, fluorescently labeled dideoxynucleotide of Example 7, Example 3 which includes the incorporation of fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator and fluorescently labeled dideoxynucleotides, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of fluorescently labeled dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

Response to Arguments:

Applicant asserts in their arguments in response to the previous final action before RCE that "neither Ronaghi et al. nor Mian et al. teach and or suggest removing excess reagents during their sequencing reaction"(Pg. 10). Applicant should note that their inclusion of this limitation in to the claims has been acknowledged, but its basis was not found in the specification as originally filed(See below new matter rejection). In addition, applicant should note that both

Ronaghi(page 87) and Mian(Col. 47) teach a step of removing or washing away reagents and further this step's inclusion in a repeated cycle of events as presently claimed by applicants.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 6, 12, 19, 20-22, 27, 28, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 19, 27, 28, and 30 are indefinite over the recitation of "the label". The phrase lacks antecedent basis as none of the preceding claims from which claim 30 depends provide antecedent basis for "the label is a fluorescent label". It is therefore unclear to which label claim 30 refers, appropriate correction is required.

B. Claims 2, 6, 12, and 20-22 are indefinite over the recitation of "double stranded" in claim 2. It is not clear how a completely double stranded sequence could be used as a template for the extension of a primer if the sequence provides no 3' overhangs for the DNA polymerase. Applicant should amend the claim to clarify the way in which extension will proceed from a totally double stranded molecule.

New Matter

5. Claims 2, 4, 6, 12, 16, and 19-31 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "removing pyrophosphate, DNA polymerase...or dideoxynucleotide" in claims 2, 4, and 19 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter. While basis was found on pages 2 and 8 of the specification for the inclusion of a step that removes or washes excess deoxynucleotide or deoxynucleotide analogue, no basis was found for the other elements, and applicant provided no guidance as to the basis for their amendment.

In addition, in the instantly rejected claims, the new limitation of "centrifugal" in claims 12 and 16 appears to represent new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter. As can be seen in the above art rejection, the examiner assumed that the inclusion of "centrifugal" was done unintentionally by applicant as they intended to recite "centripetal". While basis for "centripetal" can be found for example on page 2 of the specification, no basis was found for the limitation of a "centrifugal" force.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 12 and 16 are broadly drawn to a method wherein the microfluidic device is a disc and the fluids are moved by centrifugal force within the microfluidic device. The invention is relying on the action of a force that works only in opposition to centripetal, not one that acts on a body in motion. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification asserts that centripetal force is responsible for the "transportation of liquid" (Pg.2, line 29). However, there is no evidence in the specification, prior art, post filing date art, or Newton's Laws of physics that enables centrifugal force to act on a body of motion.

The post filing date art further confirms the unpredictability of this area. The Columbia Electronic Encyclopedia, 6th ed. defines the two forces as follows:

> **centripetal force** and **centrifugal force**, action-reaction force pair associated with circular motion. According to Newton's first law of motion, a moving body travels along a straight path with constant speed (i.e., has constant velocity) unless it is acted on by an outside force. For circular motion to occur there must be a constant force acting on a body, pushing it toward the center of the circular path. This force is the centripetal ("center-seeking") force. For a planet orbiting the sun, the force is gravitational; for an object twirled on a string, the force is mechanical; for an electron orbiting an atom, it is electrical. The magnitude F of the centripetal force is equal to the mass m of the body times its velocity squared v^2 divided by the radius r of its path: $F=mv^2/r$. According to Newton's third law of motion, for every action there is an equal and opposite reaction. The centripetal force, the action, is balanced by a reaction force, the centrifugal ("center-fleeing") force. The two forces are equal in magnitude and opposite in direction. The centrifugal force does not act on the body in motion; the only force acting on the body in motion is the centripetal force. The centrifugal force acts on the source of the centripetal force to displace it radially from the center of the path. Thus, in twirling a mass on a string, the centripetal force transmitted by the string pulls in on the mass to keep it in its circular path, while the centrifugal force transmitted by the string pulls outward on its point of attachment at the center of the path. The centrifugal force is often mistakenly thought to cause a body to fly out of its circular path when it is released; rather, it is the removal of the centripetal force that allows the body to travel in a straight line as required by Newton's first law. If there were in fact a force acting to force the body out of its circular path, its path when released would not be the straight tangential course that is always observed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant laws of physics that exist in opposition to this function attributed to centrifugal force. The time table necessary to achieve efficacious practice of this methodology as claimed would require a very large quantity of experimentation but in the end prove fruitless as the laws of Newtonian physics prohibit such an action.

Working Examples

The specification has no working examples or theoretical proofs of their aforementioned assumption for the action of centrifugal forces.

Guidance in the Specification.

The specification provides no evidence or theoretical proofs of their aforementioned assumption for the action of centrifugal forces. In addition, a thorough review of the art, both prior and post filing date, fails to show any enabled teachings.

Level of Skill in the Art

The level of skill in the art is deemed to be high practically unobtainable.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art the method relying on the use of centrifugal force to transport liquids in the present microfluidic device as claimed is not enabled. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the attribution of qualities of a centrifugal force as presently claimed. As a result given the claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art and the extraordinary mental capacities required in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

10/14/03

Sally Sakelaris

JEFFREY FREDMAN
PRIMARY EXAMINER